Investigation of the prevalence of ragweed pollen allergy and its possible risk factors in schoolchildren in Hungary

PhD thesis

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1. Introduction

Medical care of patients suffering from allergic diseases has become more important issue also in Hungary and in worldwide in the last few decades. The prevalence of atopic diseases is increasing based on several international epidemiological studies. The investigations analysing not only the prevalence of allergic diseases but also the possible factors related to them, are quite important, because causes of the rising prevalence of allergy can be evolved indirectly from these study results and the number of atopic individuals will be reduced by elimination the known harmful conditions. The National Child Respiratory Survey organised by the National Institute of Environmental Health was the first country level survey in Hungary aimed to assess the prevalence of chronic respiratory diseases and the possible risk factors associated with the development of diseases in the average school-aged child population. In my doctoral thesis I analyse the prevalence of the ragweed pollen allergy and its association with several possible perinatal and early childhood factors based on National Child Respiratory Survey data. The aim of my epidemiological investigation was to provide data for prevalence of ragweed allergy for the international literature, to identify the potential risk factors of ragweed pollen allergy in the Hungarian population, furthermore, to facilitate a better understanding of the relation of environmental and socio-economic factors impacting the development of allergy and finally to formulate recommendations for planning health promotion and preventive programs and organising targeted environmental health surveys.

2. Aims of the study

1. To investigate the prevalence and the spatial distribution (at country, regional and settlement level) of ragweed pollen allergy based on the analysis restricted to children lived at the same place from their birth by the National Child Respiratory Survey in 2005.

2. To identify the potential risk factors of ragweed pollen allergy, especially the perinatal and early childhood factors, the social-economic status of family, indoor and outdoor pollution, furthermore to investigate the associations between these factors and risk of allergy based on the analysis restricted to children lived at the same place from their birth by the National Child Respiratory Survey in 2005.

3. To analyse the spatial distribution of pollen load in the country, and to assess the associations between the long-term ragweed pollen load and lifetime prevalence of ragweed allergy restricted to children lived at the same place from their birth by the National Child Respiratory Survey in 2005.

4. To analyse the relation between long-term exposure to NO_2, SO_2, PM_{10} and the lifetime prevalence of ragweed pollen allergy based on the analysis restricted to children lived at the same place from their birth by the National Child Respiratory Survey in 2005.

5. To investigate whether some environmental factors have different effects on allergy development in Budapest and in other regions of Hungary.

6. To examine the influence of change of residence of children on the correlation between environmental factors and risk of ragweed allergy.

7. To compare the prevalence data of ragweed pollen allergy and its possible risk factors based on analysis involving all children participated in the National Child Respiratory Survey in 2005 and in 2010.

3. Material and methods

Background

The National Institute of Environmental Health carried out a country-wide cross-sectional study using a modified version of standardized questionnaires from the International Study of Asthma and Allergies in Childhood (ISAAC) in autumn of 2005, and repeated five years later in 2010 to estimate the prevalence of allergic, asthmatic and chronic respiratory symptoms and their possible risk factors among schoolchildren attending 3rd grade classes throughout the country. The core questions were translated into Hungarian and supplemented with additional questions in relation to allergy, especially factors restricted to the birth and early life circumstances, socio-economic status of family and neighbourhoods. The questionnaires were filled in by the parents in an anonymous way. The survey included 62,711 children in 2005 and 67,667 in 2010.

Study population

In each of the analysis, inclusion was restricted to 8-9 year-old children with valid data from the questionnaire filled in by parents, indicating the name or post code of settlements where the children lived.

Health outcomes

The prevalence of “parent hypothesized ragweed pollen allergy” henceforth “ragweed allergy” was determined from the responses to the question “Has your child ragweed pollen allergy?” The lifetime

prevalence of “diagnosed ragweed pollen allergy” was determined from the responses to the question “Has your child ever been diagnosed with ragweed pollen allergy by a doctor?”

Independent variables

Considering the international literature, I examined the following factors included in the questionnaire, in connection with the risk of ragweed allergy:

- gender
- age
- family history: parental atopic disease (parental allergic and/or asthma disease)
- birth and early childhood circumstances (smoking regularly during pregnancy, low birth weight, parental age at baby’s birth, serious lower respiratory tract infection in the first two years of life, unseparated child bedroom)
- socio-economic status of family: getting social aid, maternal qualification level, crowding in the house, one-parent family, unemployed parent, self-perception of living conditions, dissatisfaction with housing conditions
- potential sources of outdoor air pollution (living nearby a main road, air polluting factory/power station/bus station/landfill station not far from domicile or school)
- potential sources of indoor air pollution (natural gas stove using for cooking or heating, parental smoking, using air conditioning system, mold or moisture in the house, pet ownership)

In the survey conducted in 2010, I could only examine the following factors in connection with the risk of allergy due to using a shortened format of the questionnaire: gender, age, maternal smoking during pregnancy, serious lower respiratory tract infection in the first two years of life, crowding in the house, living nearby a main road, existing

air polluting factory/ power station/ bus station/ landfill station not far from domicile or school attended by the child, parental smoking, mold or moisture in the house

Further independent factors added to database

Population size of settlements

The data for permanent population of settlements in 2005 and in 2010 was provided by the Hungarian Central Statistical Office.

Ragweed pollen data

The airborne pollen concentration of ragweed was monitored by 19 monitoring stations of the National Aerobiological Network running according to international standards. The average sum of ragweed pollen concentration was calculated from the summed daily pollen level per each year; then these values were averaged for the years 1999-2005 and also 2004-2010 by each monitoring station. The long-term average pollen load for each settlement in Hungary and for 23 districts of capital Budapest was calculated averaging the weighted pollen load of each monitoring station as follows: the pollen load of each station was multiplied by the inverse of the square of the distance (measured in kms) of each settlement from each pollen monitoring station. The pollen exposures by settlements were put to the database containing the children's individual parameters based on the responses to the questionnaires. The long-term exposure of period 1999-2005 was added to the database created by survey in 2005 and of period 2004-2010 was added to the database based on survey conducted in 2010. The main aspect of determining the time period was to investigate the long-term effect of pollen load for developing allergy in a later age.

Air pollution exposure

The chosen indicators of exposure to traffic-related air pollution were particles with an aerodynamic diameter of 10 μm or less (PM_{10}) and gases (NO_2, SO_2). In Hungary ambient air pollution concentration of settlements were recorded by off-line manual monitoring stations of the National Immission Monitoring Network operating according to the international standards. Air pollution data belonged to only the settlements where the monitor stations were operating. Long-term exposure was calculated through 6 years averaged concentrations of each air pollutant. The air pollution concentration data of settlements were added to the database containing the children's individual parameters based on the settlement name where the children lived. The long-term exposure of period 1996-2001 was added to the database created by survey in 2005 and of period 2001-2006 was added to database based on survey conducted in 2010. The main aspect of determining the time period was to investigate the late effect of the long-term air pollution exposure exposed the children in their early childhood.

Statistical analysis

Based on the 2005 survey data, the associations between environmental exposures and the risk of ragweed allergy were analysed depending on changing in the place of residence since children' birth. The prevalence of allergy and its possible risk factors were analysed for the whole country, at NUTS2 (Nomenclature of Territorial Units for Statistics) and also at settlement levels. Descriptive statistical methods were used to present data; valid percentages were demonstrated and calculated by dividing the frequency by the total number of observations, excluding missing data, and then multiplying by 100. Chi-square and McNemar tests were applied for investigation the independence of categorical/dichotomous variables and the equality of proportions, respectively. The long-term ragweed pollen load was assessed as a continuous and categorical

variable; air pollution concentrations were treated as continuous variables. Independent two-sample t-test was used to compare the means of continuous variable among different groups; Mann-Whitney U-test was applied to compare the rank averages. The Phi coefficient was also reported beside the p-value of the Chi-square test of independence to measure the strength of the associations between the dichotomous pollutant factors. The associations between continuous variables were assessed by the Pearson correlation coefficient. Associations between different factors and lifetime prevalence of ragweed allergy were analysed by binary logistic regression models; I reported crude (cOR) and adjusted (aOR) odds ratios with 95% confidence interval (95% CI) and p values of Wald tests were presented for each factor. In the case of air pollutants, the corresponding crude and adjusted odds ratios were presented per interquartile range (IQR) increases. The multiple logistic regressions were rerun for each potential effect modifiers with the inclusion of the corresponding interaction terms to analyse potential effect modifications. I also performed generalized estimating equations (GEE) analysis with exchangeable working correlation structure to take into account the possible dependency between children living in the same settlement using the package geepack of the R statistical program. Other statistical analyses were carried out using the software IBM SPSS Statistics version 23.0. I considered a p-value less than 0.05 as statistically significant. ArcGIS software was applied for showing the distribution of ragweed allergy by NUTS2 regions. All statistical results are produced by myself. I performed the analyses for the whole country, for the rest of the country after excluding data of capital Budapest, and also separately for Budapest.

4. Results

Results of the National Child Respiratory Survey conducted in 2005

Data from 55 456 questionnaires filled in by parents of 50.8% girls, 49.2% boys were analysed after excluding those with missing answers and also those not meeting the inclusion criteria. 25 063 (46.6%) children lived in the same place from their birth. The first part of my analysis was limited to these children.

Analysis of children lived in the same place from their birth

There were highly significant regional differences ($p<0.001$) in the prevalence of diagnosed ragweed allergy in the country. Parents were more prone to indicating the prevalence of the symptoms of allergy than having a confirmation by medical examination. The prevalence of ragweed allergy hypothesized by parents was the lowest (7.0%) in the Northern Great Plain, and the highest (10.2%) in Central Hungary. The countrywide average was 8.4%. The prevalence of diagnosed ragweed allergy was significantly lower than the country average (6.6%) in the Northern Great Plain (4.7%) and in Northern Hungary (5.5%), the highest prevalence data was shown in Central Hungary (8.5%). In the capital Budapest, situated in Central Hungary, and in settlements with 50 001 population the prevalence of allergy was significantly higher ($p <0.001$) than in the rest of the country, and in small settlements. There were significant ($p<0,001$) regional differences in pollen load; it was the highest in the Northern Great Plain, and the lowest in Northern Hungary. The long-term pollen load was significantly ($p<0,001$) lower in the capital city of Budapest compared to the rest of the country, and to other cities with 50 001 population. The pollen load was significantly ($p=0,008$) lower in residences of children with ragweed allergy compared to residences of pupils without allergy at county level, but the significance lost ($p=0,473$), after excluding the children living in Budapest. There were no significant differences in air pollution between residences of

children with or without ragweed allergy. Based on the logistic regression models run at country level and also in the rest of the country after excluding data of Budapest, a positive family history was the most influential factor that increased the risk of ragweed allergy. Maternal atopic disease was a stronger risk factor than the paternal. The condition was more prevalent in boys and in children older than eight years and also in families dissatisfied with their living conditions. Further risk factors leading to allergy were also identified; as infection of the lower respiratory tract in early childhood, a separate bedroom for the child, living near to a main road or air-polluting establishments near the child's home or school. On the other hand, in the case of parents with lower social status or families using gas stoves for cooking or heating, the prevalence of allergy was considerably lower. Exposure to domestic animals in early childhood also decreased the risk of the condition. Comparing the pollen load and the children's allergy risk, I could not establish any dose-effect relationship between these two factors, only in the pollen exposure category of 7501-9500 pollen grains/m^3 category was a significant negative relation between pollen load and risk of allergy. Based on my analysis, long-term exposure to NO_2, SO_2, and PM_{10} did not increase the risk for ragweed pollen allergy significantly. The gender, parental atopic status and lower respiratory tract infection was a significant effect modifier for the risk of allergy. Low birth weight, parental age at baby's birth, using air conditioning system, using gas water heater in the bathroom, living conditions considered by family bad or very bad, single-parent family, mold or moisture in the house showed a non-significant association with allergy. I could identify some factors having different effects on allergy development in Budapest compared to other regions of Hungary. Only the parental atopic status and pet ownership showed significant relationships with risk of allergy in children lived in the capital city.

Analysis of the correlation between change of residence and allergy risk factors in those children who had moved from their place of birth

The second part of my analysis focused on those 28,679 children who moved from their place of birth. The prevalence of diagnosed ragweed allergy (7.1%) was significantly larger ($p=0.024$) in those children who changed residence compared to those lived in their place of birth. The prevalence of familial atopy and infection of the lower respiratory tract in early childhood was also higher, even though their social situation was more stable. Based on the logistic regression model with complex sampling, the effects of the factors not influenced by the relocation, the factors proved to be strong ($p< 0.001$) in every model (sex, age, familial atopy, infection of the lower respiratory tract, separate bedroom), and further factors as smoking during pregnancy, using gas stove or the presence of pets showed no difference between the two groups in terms of allergy risk. On the other hand, I found different effects on the risk of allergy between those who relocated and those who did not in the following factors: social situation, garbage landfill near the residence, mould stains in the residence, pollen exposure and air pollution.

Comparing the results of the 2005 and 2010 National Child Respiratory Surveys

Following the data cleaning, I included 55,795 children (51.7% girls, 48.3% boys) in the analysis of the 2010 data. The prevalence of diagnosed ragweed allergy in 8-9 year old children did not change significantly between the two surveys (6.9% vs. 7.0%, $p=0.402$). There were two regions where a significant change occurred: the prevalence decreased in South Transdanubia and increased in the Northern Great Plain compared to the data from five years before. The prevalence decreased in Budapest (10.4% vs 8.7%, $p<0.001$). The proportion of medical diagnoses corroborating the parental diagnosis of allergy was higher in every region in 2010 than it was in 2005. Pollen exposure was significantly lower ($p<0.001$) at national level in the 2004-2010 period than in the 1999-2005 period. Apart from Central Hungary, pollen exposure was lower in every region during the 2004-2010 period, than previously but in Central Hungary the pollen exposure

was significantly higher. The effects of perinatal and living environment factors on the allergy risk showed no significant difference between the two surveys. There is no discernible dose-response relationship between pollen exposure, air pollution and allergy risk, but the inclusion of children who relocated and those who did not in the same model resulted in the contrary effect when correlating environmental exposure and allergy risk factors.

5. Discussion

Based on the National Child Respiratory Surveys conducted in 2005 and 2010, the following conclusions can be drawn:

1. Analysing the data of 8-9 year old children who spent their childhood in the same residence from their birth, significant regional differences were found in the prevalence of ragweed allergy, however, dose-response relationship with ragweed pollen load could not be stated. While the pollen exposure was high in the Great Plain and Southern Transdanubia, the prevalence of allergy was considerably lower in these regions than the national average. Based on my investigation, this phenomenon can be explained partly by the deprivation of these regions. The territorial differences (both regional and in the size of community) in the prevalence of ragweed allergy showed correlation with socio-economic factors. There was a significant difference between the rates of proper medical diagnoses and the suspicion of the parents related to their children' ragweed allergy. It might be explained by the misclassification/neglecting of symptoms of hay fever by the parents not being aware of the problem; or by not contacting the local health service after a correct parental observation. This latter reason might contribute to the lower prevalence in some regions, as there is no proper medical diagnosis of the disease. I could extend my analysis regarding the accessibility of special health care availabilities at regional level. Such an analysis would be of high importance.

2. The analysis also proved that genetic factors and genomic imprinting should also be considered as predicting factors in the development of ragweed allergy. Compared to previous studies, this paper introduced the analysis of the interactions of allergy risk factors, which further highlighted that the same environmental factor has different effects on genetically different individuals. In concert with the existing literature, I also found that there was a male dominance in the prevalence of ragweed allergy. The interconnection between infection of the lower respiratory tract in early childhood, a separate bedroom for the child versus overcrowded living spaces, the presence of a pet and the risk for allergy might validate the assumptions about hygiene and microbiomes. Socio-economic circumstances associated with the lower educational level of the parents and, as a consequence, with reluctance to access health services, the lack of proper medical diagnosis can explain the lower prevalence of allergy in disadvantaged regions. Several international studies highlighted the risk-increasing effect of air pollution. This conclusion was also verified in this present paper; the air pollution indicator factors (main road, air polluting establishment) showed positive correlation with the prevalence of allergy.

3. In the target period (1999-2005), a significant positive correlation between pollen exposure and the risk of allergy could not be established. It might be explained by the fact that the total average pollen amount of ragweed exceeds many times that threshold level which provokes allergic reaction in those predisposed to the illness. Thus the pollen exposure was so high in the analysed range – including the reference category – that it could not have a further risk effect in the development of allergy.

4. Based on my analysis, long-term exposure to NO_2, SO_2, and PM_{10} does not increase significantly the risk of ragweed pollen allergy. This finding can be explained by the SO_2 concentration, which was remarkably lower in the investigated time period and area. In the case

of, NO_2 and PM_{10}, the reason behind the inconclusive correlation might be the specificity of data collection.

5. It was also established in my paper that some factors had different effects on allergy development in Budapest and in other regions of Hungary. This effect can be observed in cases of statistically strong factors, which also corroborates the assumption that the children living in Budapest should be examined in a separate study in order to eliminate the distorting effect of their data.

6. My paper is the first in Hungary to examine the influence of change of residence on the correlation between environmental factors and risk of allergy. The prevalence of ragweed allergy and the risk-increasing effect of some factors significantly differed between those children who had lived in the same place since their birth and those who had changed residence. There was no discernible difference in the effect of those statistically strong factors that were independent of residence; while those environmental circumstances that changed significantly with the change of residence – e.g. long-term exposure to pollen and air pollution – showed a serious difference in relation to the prevalence of allergy in children who had and children who had not changed residence. These results also support the assumption that the effect of a certain environmental factor on the later development of allergy depends on the time of exposure in early childhood or later. Thus it can be stated that change of residence is a vital element in the examination of the effect of environmental exposure on allergy, those who live in the same residence from their birth can provide more reliable results.

7. Based on the results of the National Child Respiratory Surveys conducted five years apart, there was no significant difference in the prevalence of ragweed allergy in 8-9 year old children between the two periods. According to the data of all the children included in the surveys, the prevalence of diagnosed ragweed allergy was 6.9% in 2005 and 7% in 2010 in Hungary – this prevalence is similar compared

to other European countries. There were two regions where a significant change occurred: the prevalence decreased in South Transdanubia and increased in the Northern Great Plain. The prevalence in Budapest in 2010 was significantly lower than 5 years earlier; while in other bigger towns and smaller communities, the prevalence remained consistent. The analysis of the data recorded in 2005 and 2010 provided similar results in terms of the correlation between risk factors and prevalence of allergy. It is important to emphasise that the two surveys were two cross-sectional examinations conducted in two different time periods, in different population. Theism type of study cannot be used to clarify cause-effect relationship; the findings should be tested in further analytical epidemiological studies.

Suggestions for possible use of the results

As it has been established, the development of allergic diseases is influenced by a combination of several environmental and other factors. This present epidemiologic analysis on the one hand confirmed several results published in international papers, furthermore, it also drew attention to the specificities of the situation in Hungary. The results can be used by the Institutes of Health Promotion throughout the country for developing prevention programs. First and foremost, through health promotion programs and preventive activities carried out by the district nurses in less developed regions, the awareness and knowledge of parents can be increased concerning the recognition of the symptoms of hay fever and, the possible treatments, and complications of the untreated cases. The nurses can enhance the compliance of parents with doctors. As early as during pregnancy the nurses can give advices for high risk parents - babies, how to lower the risk of development of allergic diseases in babies and early childhood. As a primary preventive initiative, parents should be warned about the dangers of smoking during pregnancy and of excessive hygienic practices. It is also important to advocate for

breast feeding exclusively until the age of six month and to avoid unnecessary antibiotic treatment in early childhood. The parents and children should be educated about allergens in the environment with special regard to ragweed. Calling the attention to low-allergen, clean, surroundings can also be a useful measure.

The risk factors defined in the study are not only essential for public health professionals but also for paediatricians and doctors in all professional specialties dealing with allergic diseases as well. For effective prevention, environmental factors increasing the prevalence of allergy should be widely known together with targeted actions decreasing the effect risk factors. The impact of prevention can be summarised with the following quote: **"You should change when it is not necessary; for when it is necessary, it is already too late."**

6. List of own publication

Original publications on the topic of the dissertation:

Vörös K, Kói T, Magyar D, Rudnai P, Páldy A. (2019) The influence of air pollution on respiratory allergies, asthma and wheeze in childhood in Hungary. Minerva Pediatrica, In Press (2019) doi: 10.23736/S0026-4946.19.05466-5. (**IF: 0,832**)

Vörös K, Bobvos J, Varró JM, Málnási T, Kói T, Magyar D, Rudnai P, Páldy A. (2018) Investigation of the impacts of long-term ragweed pollen load and other potential risk factors on ragweed pollen allergy among schoolchildren in Hungary, Ann Agric Environ Med, 25(2):307-313. (**IF: 1,030**)

Vörös K, Bobvos J, Varró MJ, Málnási T, Kói T, Magyar D, Rudnai P, Páldy A. (2018) A hosszú távú pollenterhelés és légszennyezettség hatásának vizsgálata a parlagfűpollen-allergia előfordulási gyakoriságával összefüggésben, EgTud, 62(1): 58-84.

Other publications, not in the dissertation topic:

Tischner Zs, Kredics L, Marik T, **Vörös K**, Kriszt B, Péter B, Magyar D. (2019) Environmental characteristics and taxonomy of microscopic fungi isolated from washing machines. Fungal Biology, 123:650-659. (**IF:2,699**)

Tischner Zs, Kredics L, Marik T, **Vörös K,** Magyar D. (2019). Hazai háztartásokban üzemelő mosógépek gombaszennyezettsége a használati szokások tükrében (Fungal contamination of washing machines in domestic households in the light of usage habits) EgTud, 63(1-2): 45-65.

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Törő K, **Vörös K**, Mészner Z, Váradi-T A, Tóth A, Kovács K. (2015) Evidence for infection and inflammation in infant deaths in a country with historically low incidences of sudden infant death syndrome. Front Immunol.6:389, (**IF:5,695**)

Vörös K, Cser V, Törő K. (2012) A nozokomiális infekciók szerepe a morbiditásban és letalitásban, különös tekintettel a multirezisztens Acinetobacter baumannii által okozott infekciókra. Med Univ, 45;4:139-148.